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## Neurons in the dorsal column nuclei of the rat emit a moderate projection to the ipsilateral ventrobasal thalamus

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**Abstract** The dorsal column nuclei (DCN; gracile and cuneate nuclei) give rise to the medial lemniscus, the fibre system that provides an organised somatosensory input to the thalamus. Unlike the spinothalamic and trigeminothalamic tracts that project, also to the ipsilateral thalamus, the medial lemniscus system is believed to be entirely crossed. We demonstrate that DCN emit a small number of axons that reach the ipsilateral thalamus. As retrograde fluorescent neuronal tracer Fluorogold was stereotaxically injected in the ventrobasal thalamus of nine young adult Wistar rats. The injection foci were voluminous and encroached upon adjacent nuclei, but the periphery of the injection halo never spilled over to the contralateral thalamus. All sections of the contralateral gracile and cuneate nuclei and the midline nucleus of Bischoff contained abundant retrogradely labelled neurons. The comparison with the Nissl-stained parallel sections suggests that approximately 70–80% of the DCN neurons project to the contralateral thalamus. Counting of retrogradely labelled neurons in two cases revealed 4,809 and 4,222 neurons in the contralateral and 265 and 214 in the ipsilateral DCN, respectively. Thus, although less prominent than the ipsilateral spinothalamic tract, the lemniscal system also emits an ipsilateral projection that accounts for about 5% of the neuronal population in DCN that innervates the ventrobasal thalamus.

**Keywords** Gracile nucleus · Cuneate nucleus · Medial lemniscus · Ventral posterolateral thalamic nucleus · Ventral posteromedial thalamic nucleus · Somatosensory system

**Abbreviations** AP: Area postrema · Bi: Midline nucleus of Bischoff · Cx: Cerebral cortex · DCN: Dorsal column nuclei · Gr: Gracile nucleus · Cu: Cuneate nucleus · CuC: Cuneate nucleus, caudal part · CuM: Cuneate nucleus, medial part · CuR: Cuneate nucleus, rostral part · Hip: Hippocampus · Ic: Internal capsule · PC: Paracentral thalamic nucleus · Po: Posterior thalamic nuclear group · Sol: Nucleus of solitary tract · Sp5C: Spinal trigeminal nucleus, caudal part · VPM: Ventral posteromedial thalamic nucleus · VPL: Ventral posterolateral thalamic nucleus · Z: Nucleus Z · Zi: Zona incerta · 3V: Third ventricle

### Introduction

The dorsal column nuclei (DCN) receive somatotopically arranged primary afferent fibres, contain a representational map of the trunk and limbs, and give rise to the medial lemniscus, the pathway that provides fast, precisely organised somatosensory input to the thalamus (Foerster 1936; Poggio and Mountcastle 1960; Brodal 1981; Mountcastle 1984; Smith and Deacon 1984; Jones 1985; Berkley et al. 1986; Kaas and Pons 1988; Florence et al. 1989; Snow and Wilson 1991; Tracey and Waite 1995; Parent 1996; Xu and Wall 1996, 1999; Bermejo et al. 2003; Willis and Coggeshall 2003; Kaas 2004). In addition to the primary afferent input from the mechanoreceptive spinal ganglia pseudounipolar neurons, the DCN neurons are innervated by so called “post-synaptic fibres”, emitted from neurons in the spinal dorsal horn, and around the canalis centralis (Petit 1972; Rustioni 1977; Rustioni and Kaufman 1977; Rustioni et al. 1979; Bennett et al. 1983; Cliffer and Willis 1994; Hirschberg

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et al. 1996). These fibres provide mainly a visceral nociceptive input that is conveyed to the contralateral thalamus via the medial lemniscus (Al-Chaer et al. 1996a, 1996b, 1998; Nauta et al. 2000; Willis and Westlund 2001, 2004; Willis and Coggeshall 2003).

Numerous anterograde tracing studies (using Marchi-technique, silver impregnation, autoradiography, WGA-HRP, PHA-L, electron microscopy) and retrograde tracing studies (using HRP, fluorescing tracers) pointed out that the projection of DCN axons to the thalamus is entirely crossed (Edinger 1885, 1889; Tschermak 1898; Probst 1900; Walker 1938; Rasmussen and Peyton 1948; Matzke 1951; Lund and Webster 1967; Ralston 1969; Boivie 1971, 1978; Norton and Kruger 1973; Groenewegen et al. 1975; Hand and van Winkle 1977; Berkley and Hand 1978; Blomqvist et al. 1978, 1985; Berkley et al. 1980, 1986; Blomqvist 1980; Feldman and Kruger 1980; Kalil 1981; Bull and Berkley 1984; Jones 1985; Massopust et al. 1985; Peschanski et al. 1985; Ma et al. 1987; Berkley and Vierck 1993; Ralston and Ralston 1994; Ralston et al. 1996; Li and Mizuno 1997a, 1997b). First, Granum (1986) noticed ipsilateral DCN-thalamic neurons, but her attention was focussed on the spinothalamic tract. However, also in the painstaking retrograde tracing study of Kemplay and Webster (1989) on the DCN- and trigeminothalamic projections, the ipsilateral connection was also only briefly mentioned: "Ipsilaterally projecting labelled neurons were occasionally seen in the present study". Recently, Bermejo et al. (2003) considered the ipsilateral DCN-thalamic projection as insignificant.

Here, we present data that a moderate but constant ipsilateral projection to the thalamus arises from both DCN, nucleus gracilis (Gr) and nucleus cuneatus (Cu).

## Materials and methods

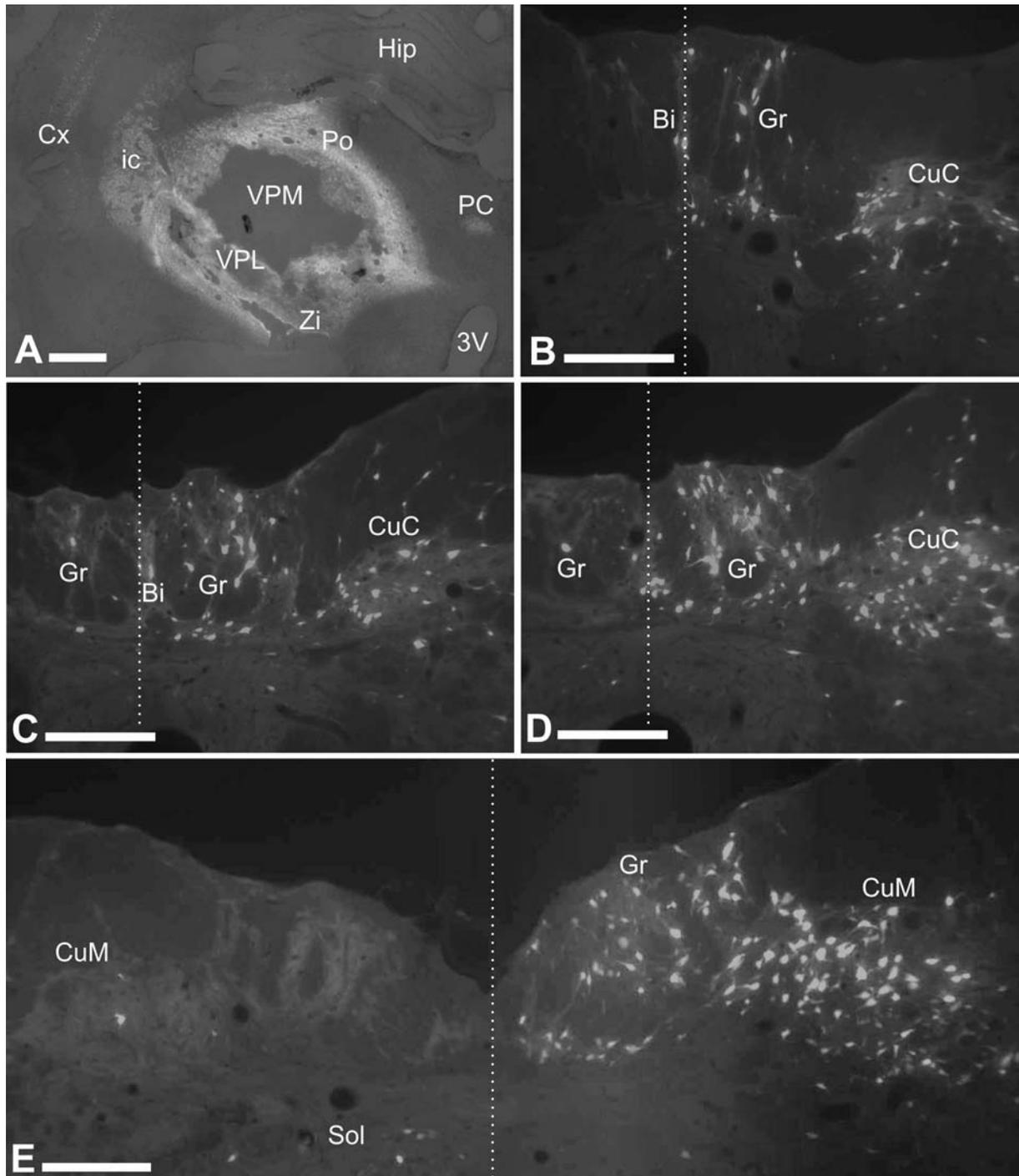
Nine young-adult Wistar rats, weighing 260–320 g were used. The experiments were carried out following the German regulations on animal welfare in conformance to National Institutes of Health guidelines. Under deep anaesthesia (Pentobarbital- $\text{Na}^+$ , 40 mg/kg), the animals received unilateral stereotaxic injection in the ventrobasal thalamus of the fluorescing tracer Fluoro-gold (Fluorochrome, Denver, USA). Using 2% Fluoro-gold injections (pH 7.0, solved in physiological saline), one focus of 1  $\mu\text{l}$  was centred in the ventrobasal thalamus; coordinates from bregma and midline: AP  $-3$ , L 2.8 (Paxinos and Watson 1998). The survival time was 5–6 days. The animals were then deeply anaesthetised and perfused transcardially with 100 ml phosphate buffered saline, followed by 500 ml 4% paraformaldehyde in phosphate buffer (pH 7.2), and finally with 100 ml of the same fixative to which 5 g sucrose was added. The brains were removed and stored in 20% sucrose in the same fixative for 2–30 days at 4°C. Serial sections, 30  $\mu\text{m}$  thick, were cut on a freezing microtome and stored in phosphate buffer overnight. Through the injection site,

every third section was spared and was alternately either mounted for observation in the fluorescent microscope, or stained with cresyl violet for cytoarchitectonic orientation. The sections for fluorescence observation were stored at 4°C, in dark. Through the caudal medulla, all sections were spared, and in most cases every fifth section was Nissl stained, while the remaining sections were mounted and allowed to dry overnight. They were dehydrated in ethanol, cleared in xylene, and covered with Entellan. In two rats, all sections through the caudal medulla were prepared for observation in the fluorescent microscope. In these two cases, all sections were photographed and the retrogradely labelled contralateral and ipsilateral DCN neurons were counted. The sections were observed with a Leitz Aristoplan fluorescent microscope, equipped with a filter set with excitation wavelength 350–395 nm. Photomicrographs of selected fields were taken with a digital camera (7.3 Three Shot Colour, Visitron Systems, Diagnostic Instruments).

## Results

Although Fluoro-gold is an excellent retrograde tracer (Choi et al. 2002), a shortcoming of it is that it spills broadly in the injected tissue. Following slightest encroachment of the Fluoro-gold halo upon the thalamic midline, the case was excluded from examination. Such were two cases, although the pattern of retrograde labelling of DCN was not affected. The successful injections were also large (Fig. 1a) and involved completely the ventroposterolateral (VPL) and ventroposteromedial (VPM) thalamic nuclei, as well as large portions of the posterior thalamic nuclear group. The largest injections reached caudally the rostral poles of the medial geniculate body and anterior pretectal nucleus, and rostrally the ventral anterior thalamic nucleus. As a rule, the lateral border of the injection focus involved the reticular thalamic nucleus, and the ventral border involved the terminal part of the medial lemniscus and the dorsal zona incerta. Rostroventromedially the largest injection foci reached the ventromedial and ventrolateral thalamic nuclei, medially the paracentral and central lateral thalamic nuclei and caudomedially the parafascicular thalamic nucleus. Dorsally, the regions of the laterodorsal thalamic nucleus, surrounding the needle track were differently involved in various experiments.

All sections of the contralateral Gr and Cu contained abundant retrogradely labelled neurons (Figs. 1b–e, 2b–f). The comparison with Nissl-stained parallel sections suggests that approximately 70–80% of the DCN neurons project to the contralateral thalamus. About 20–30% of the DCN neurons were not retrogradely labelled. Only a part (8–10%) of those Nissl-stained neurons in DCN were small, pale cells that are most probably interneurons (Barbaresi et al. 1986; Popratiloff et al. 1996), so that the remaining appear to be extra-



**Fig. 1** **a** The injection focus of Fluoro-gold in the thalamus (*Po* posterior nuclear group, *VPM* ventral posterolateral nucleus, *VPL* ventral posteromedial nucleus) at a maximum extent encroaches ventrally upon zona incerta (*Zi*) and laterally reaches the internal capsule (*Ic*). For orientation, positions of cortex (*Cx*), hippocampus (*Hip*), paracentral nucleus (*PC*) and third ventricle (*3V*) are indicated. **b–e** Microphotographs of retrogradely labelled DCN neurons of its caudal third. The medulla contralateral to the injection is on the right of the figures, the ipsilateral on the left, the midsagittal plane indicated by *dashed lines*, position of the sections are indicated in Fig. 2a. **b** DCN near their caudal pole, gracile nucleus (*Gr*), caudal cuneate nucleus (*CuC*), midline nucleus of Bischoff (*Bi*). **c, d** More rostrally, several ipsilaterally projecting neurons in the caudal portion of *Gr*. **e** In the most ventral part of the ipsilateral medial cuneate nucleus (*CuM*) a single labelled neuron is seen, further labelled neurons of the ipsilaterally projecting solitariiothalamic tract (*Sol*). Scale bars = 250  $\mu$ m

thalamic projection neurons. A moderate number of ipsilaterally labelled DCN neurons was established in all cases with unilateral thalamic injections (Figs. 1c–e,

2b–f). A bilateral, mainly contralateral labelling was observed also in the spinal cord and in the sensory trigeminal nuclei. In some cases, the tracer halo reached

the most medial portion of the VPM, and in these experiments also neurons in the rostral portions of the solitary nucleus were labelled, ipsilateral to the injection (Figs. 1e, 2f). Ipsilateral DCN-thalamic neurons were scattered throughout the Gr and Cu. Nearly 40% of the sections examined displayed retrogradely labelled neurons in the ipsilateral Gr, and approximately 15% of the sections contained ipsilateral Cu-thalamic cells. Such neurons were few (1–3 per section, occasionally 4–5), while in the contralateral DCN the number of labelled neurons regularly exceeded 40 per section. The large majority of the ipsilaterally projecting cells were of the same size of the Gr and Cu neurons projecting to the contralateral thalamus. There was a clear tendency in the location of the ipsilaterally projecting neurons: they were found predominantly in the peripheral portions of the Gr and Cu, and especially in the ventral portions of these nuclei.

On Figs. 1b–e and 2b–f, a series of microphotographs of the DCN is presented, their position being indicated in Fig. 2a. The injection focus of this experiment is shown in Fig. 1a. This is one of two cases in which all sections in the caudal medulla were processed for fluorescence, and the labelled cells were counted. On Fig. 1b, the DCN complex near its caudal pole is presented at the spinomedullary junction. The vertical strand of neurons represents the nucleus of Bischoff: a small, midline neuronal group, clearly outlined only in rodents and lagomorphs (Kemplay and Webster 1989; Bermejo et al. 2003). Lateral to it, surrounded by the fibres of fasciculus gracilis lies the most caudal part of Gr that also represents a dorsoventrally oriented strand of elongated neurons. More lateral is the caudal division of Cu (CuC). At the caudal pole of DCN complex occasional ipsilaterally projecting neurons are seen, always in Gr. Moving rostrally (Fig. 1c, d), the nucleus of Bischoff gradually disappears, and the ipsilaterally projecting neurons in Gr are more common. On the more rostrally following sections (Figs. 1e, 2b), ipsilaterally projecting neurons are seen in the medial division of Cu (CuM). At the level of the caudal end of area postrema (Fig. 2c) and in the following sections (Fig. 2d, e), the ipsilaterally projecting neurons are common. Near the rostral pole of DCN complex, it is presented by the rostral division of Cu (CuR). Here, also ipsilaterally projecting cells are seen (Fig. 2f). Additionally, some retrogradely labelled neurons were found in the contralateral external cuneate nucleus, corroborating recent descriptions of Bermejo et al. (2003).

In the case described (Figs. 1, 2), the contralateral DCN contained 4,809 labelled neurons, and in the ipsilateral DCN 265 labelled neurons were observed. In the second case, the injection focus of Fluoro-gold was placed slightly more caudomedially, and the rostral pole of VPL (AP  $-2.2$ – $2.0$ , see Fig. 28 in Paxinos and Watson 1998) was not infiltrated. Here, the contralateral DCN contained 4,222 fluorescing neurons, and 214 neurons were labelled in the ipsilateral DCN. Probably due to the significant involvement of the most medial

(parvocellular) part of VPM, the number of labelled neurons in the ipsilateral solitary nucleus was larger (not illustrated).

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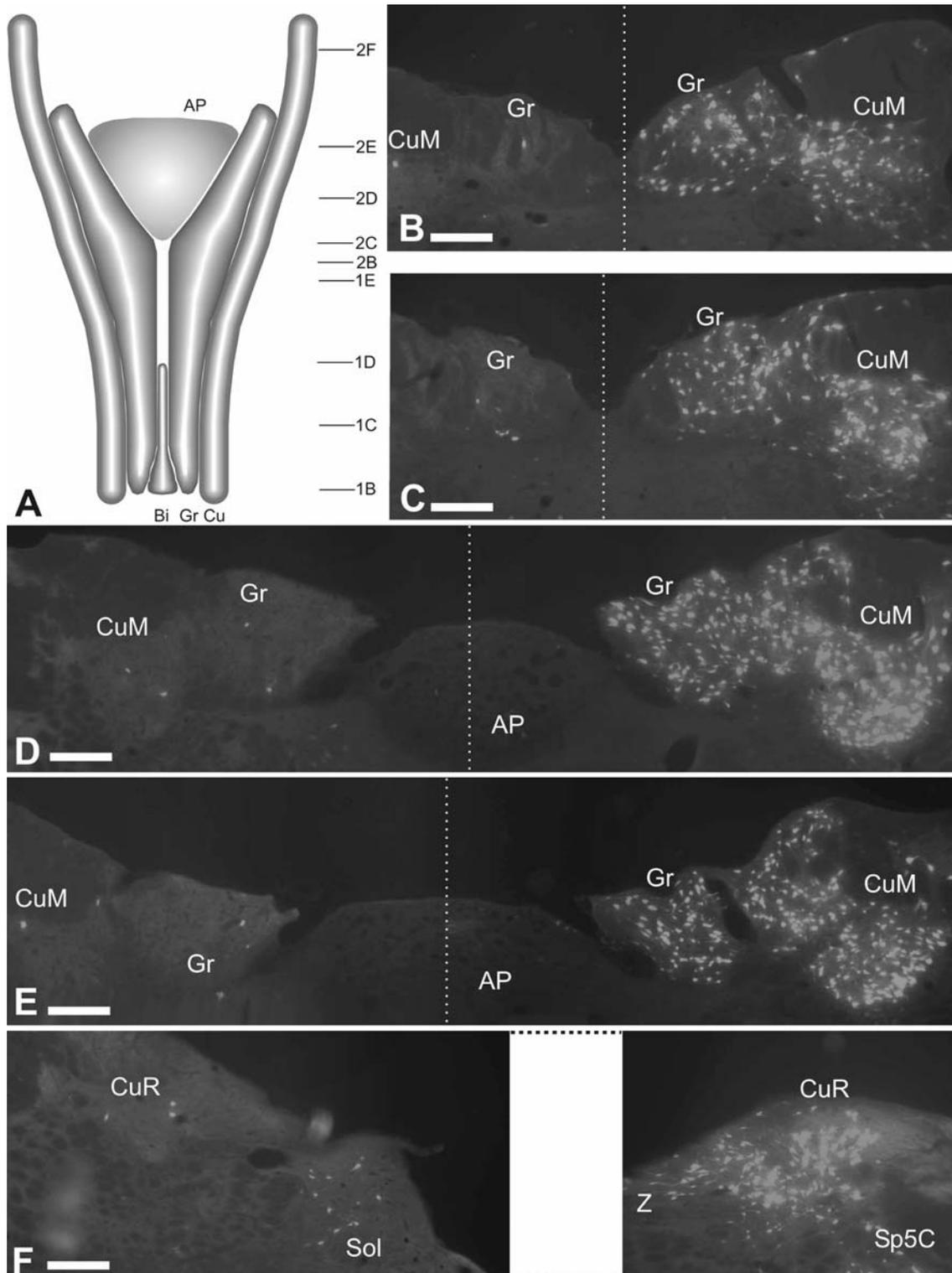
## Discussion

We report the existence of a moderate but constantly detectable projection to the ventrobasal thalamus, arising in the ipsilateral DCN. It accounts for about 5% of the neuronal population of DCN that innervates the ventrobasal thalamus. Since in the calculation the midline nucleus of Bischoff was not involved, the portion of ipsilaterally projecting cells from the total thalamopetal population appears to be very slightly smaller as the number of the labelled Bischoff's cells did not exceed 70 in neither cases.

In most cases, the ipsilaterally projecting neurons are smaller than the largest contralaterally projecting cells, located usually in the “core clusters” (Berkley et al. 1986; Bermejo et al. 2003) of both DCN. The ipsilaterally projecting neurons are more uniformly distributed in Gr, and are seen through its entire rostrocaudal extent. Most often such neurons are found near the ventral and medial border of the nucleus. In Cu, the distribution of ipsilaterally projecting neurons is very uneven. CuC almost lacks such neurons, while in CuM and CuR they are a common finding. In the rostral Gr, in CuM, and especially in CuR, there is a clear tendency for the clustering of ipsilaterally projecting neurons.

The two other major somatosensory thalamopetal systems also emit ipsilateral connections. An ipsilateral spinothalamic tract was reported in the rat (Burstein et al. 1990; Usunoff et al. 1999), and clinical observations indicate that ipsilaterally projecting spinothalamic neurons exist also in humans (reviewed by Nathan et al. 2001). In the rat, the ipsilateral spinothalamic projection is significant: according to Burstein et al. (1990), the ipsilaterally projecting cells are approximately 10% of the total spinothalamic neuronal population. The trigeminothalamic connection is also bilateral, but especially for the spinal trigeminal nucleus, it is strongly crossed (Kemplay and Webster 1989; Usunoff et al. 1997; Waite and Ashwell 2004).

At present, no plausible speculations on the functional significance of the ipsilaterally projecting DCN neurons could be suggested. It is more and more evident that the DCN are not only an accurate (fast conducting, precisely somatotopically organised), but also not a simple relay station in the exospino–bulbo–thalamo–cortical mechanoreceptive neuronal chain. As pointed out by Al-Chaer et al. (1998), Nauta et al. (2000) and Willis and Westlund (2001, 2004), along the primary afferent fibres, the DCN receive also a nociceptive input from the postsynaptic afferent fibres. Further, along the mighty projection to the VPL, the DCN innervate also a large number of functionally diverse brain areas: posterior thalamic nuclear group, zona incerta, pretectal nuclei, inferior and superior



**Fig. 2** **a** Schematic dorsal view of the gracile (*Gr*) and cuneate (*Cu*) nuclei, the midline nucleus of Bischoff (*Bi*) and the area postrema (*AP*) indicating the position of sections as shown in Figs. 1b–e and 2b–f. **b–f** Serial sections through the middle (**b**, **c**) and rostral portions (**d–f**) of DCN complex, the medulla contralateral to the injection is on the right of the figures, the ipsilateral on the left, the midsagittal plane indicated by *dashed lines*. **b** Two ipsilaterally projecting neurons; one is in gracile nucleus (*Gr*), and one in the ventral portion of medial cuneate nucleus (*CuM*). **c** Group of ipsilaterally projecting neurons in the basal part of *Gr* and in *CuM*. **d**, **e** At the levels of *AP* several ipsilaterally projecting neurons in the rostral portion of *Gr* and in *CuM*. **f** Abundant contralaterally projecting neurons are seen in the rostral cuneate nucleus (*CuR*) and in the caudal spinal trigeminal nucleus (*Sp5C*). The medially directed “wedge” of labelled neurons belongs to nucleus *Z* (*Z*). To the left three-labelled neurons in the ipsilateral *CuR*. A group of labelled neurons in the nucleus of the solitary tract (*Sol*) is also seen. Scale bars = 250  $\mu$ m

colliculi, red nucleus, substantia nigra, pontine nuclei, inferior olive, cerebellum, cochlear nuclei, and the spinal cord (Boivie 1971; Cheek et al. 1975; Groenewegen et al. 1975; Burton and Loewy 1977; Hand and van Winkle 1977; Berkley and Hand 1978; Blomqvist et al. 1978; Edwards et al. 1979; Berkley et al. 1980, 1986; Feldman and Kruger 1980; Somana and Walberg 1980; Swenson and Castro 1983a, 1983b; Bjorkeland and Boivie 1984; Bull and Berkley 1984; Mantle-St. John and Tracey 1987; Kosinski et al. 1988; Paloff and Usunoff 1992; Usunoff and Paloff 1992; Li and Mizuno 1997a, 1997b; Bermejo et al. 2003). The cells of origin of the projections that are not collaterals of the thalamopetal axons (see below) are located usually in the peripheral “shell” of both DCN, while the bulk of the DCN neurons that innervate the thalamus occupy the “core” of DCN (reviewed in Berkley et al. 1986; Bermejo et al. 2003). Thus, many of the presently described ipsilaterally projecting neurons are located in the “extrathalamic territory” of the DCN. These pathways might be separated in two groups. Most of the projections arise from separate neuronal populations (Berkley et al. 1980, 1986; Bull and Berkley 1984; Mantle-St. John and Tracey 1987). On the other hand, neurons innervating VPL were demonstrated to emit divergent collaterals to the pontine nuclei (Kosinski et al. 1988), to the inferior colliculus (Li and Mizuno 1997a), to the cochlear nuclei (Li and Mizuno 1997b), and even to the spinal cord (Bermejo et al. 2003).

Further investigations should unravel (1) the eventual differences in the afferent connectivity of “classical” contralaterally projecting neurons and the presently described moderate, ipsilaterally projecting neuronal population, and (2) whether these neurons, besides projecting to the ipsilateral thalamus, provide an afferent input to the other brain areas.

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